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FROM THE ALLERGY DIVISION OF THE JEWISH HOSPITAL OF BROOKLYN

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ASTHMA AND HAY FEVER

The Repository Method for the Treatment of Ragweed Pollinosis (1959): A Cooperative Study Involving 1,218 Patients. Furstenberg, F. F.: Ann. Allergy **18**: 866, 1960.

Twelve hundred and eighteen patients with ragweed pollinosis, most of whom had previously been treated by conventional methods, were subjected to repository treatment. The techniques employed were those suggested by Loveless or Brown or modifications of these methods. Twenty-three physicians participated in this study and administered doses ranging from 300 P.N.U. to 15,000 P.N.U. They reported that they had encountered 76 systemic reactions which lasted anywhere from a few hours to one or two days. There were 28 local reactions. Systemic reactions occurred more frequently in previously untreated patients and could not be correlated with the size of the dose or the degree of skin or ophthalmic reactivity. In few instances the quality of the emulsion could be incriminated as the cause of reactions. No local abscesses were encountered. Previously untreated patients had "decidedly more reactions." Seven physicians treating 849 patients encountered 25 systemic reactions (3 per cent) and 16 physicians treating 367 patients encountered 51 systemic reactions (14 per cent). Some patients were simply switched from conventional treatment to a single repository injection. According to the author, clinical results were "as good as those which result from injections of unemulsified pollen extract." Dosage did not appear to influence the results of therapy. E. K.

Asthma Secondary to Cardiospasm. Henderson, L. L., and Olsen, A. M.: Ann. Allergy **18**: 266, 1960.

Asthma apparently resulting from cardiospasm was observed in a 36-year-old man who gave a history of coughing, wheezing, and exertional dyspnea, worse at night, for the past 7 years. He also had perennial rhinitis. For 4 years he complained of a sense of substernal fullness after meals and occasionally regurgitated small amounts of food. X-ray examination demonstrated a widening of the upper mediastinum. Barium swallow revealed failure of barium to enter the stomach. Surgical correction of esophageal obstruction gave complete relief of respiratory symptoms for a 5-month period of observation. E. K.

Clinical Use of Glutamates (Capomate) in the Treatment of Resistant Bronchial Asthma. Epstein, I. S.: Ann. Allergy **18**: 754, 1960.

Asthmatic sputum has about double the potassium content of nonasthmatic sputum and the potassium levels decrease when clinical improvement occurs. It was postulated that potassium loss into the sputum reflected increased permeability of the bronchial cell wall. Calcium glutamate, administered daily, decreased the potassium concentration in bronchial secretions but calcium gluconate had no effect. Glutamate has been shown to decrease potassium loss from brain slices. Sixteen asthmatics, refractory to the usual treatment, were given 350-700 mg. calcium glutamate and 150-300 mg. potassium glutamate orally 3 or 4 times daily, the dose being adjusted according to the patient's need. In 3 patients observed for 5 years, there were still demonstrable beneficial effects. Most of the patients experienced at least slight improvement and relapse occurred on withdrawal of the medication or substitution of a placebo. Mucous viscosity was reduced and vital capacity increased. Improvement was noted in from 1 to 3 weeks. E. K.

The Effect of Gamma Globulin in Asthmatic Children. Brown, E. B., and Botstein, A.: New York J. Med. **60**: 2539, 1960.

A group of 29 children, ranging in age from 1 to 10 years, all of whom had a history of asthma of at least one year's duration were treated with gamma globulin. In each case the acute attack was usually preceded by a febrile upper respiratory infection. Each child had a complete allergic work-up and gamma globulin blood levels were determined prior to starting the study. Offending allergens were eliminated but specific hyposensitization therapy and prophylactic antibiotic therapy were discontinued during the period of observation. The only therapy administered, other than gamma globulin, was symptomatic treatment for relief of acute episodes of wheezing. Each youngster was given 0.15 c.c. of gamma globulin per pound of body weight intramuscularly every 3 weeks. After 9 months those youngsters who had not responded to treatment satisfactorily were given an increased amount of gamma globulin (0.2 c.c. per pound of body weight). Fourteen of the 29 children obtained excellent results. Eleven out of the 14 were on the smaller dose of gamma globulin. Out of 9 children who were improved, 3 experienced this change only after the dosage of gamma globulin was increased. Six of the 29 patients had poor results. The average age of the patients with the most successful results was 5 years whereas the average age of those who failed to respond was 7½ years. This indicated that the earlier treatment is instituted the better the result. Children with negative skin tests to the common inhalants responded well to gamma globulin. The poorest response was observed in youngsters with multiple sensitivities. There was a noticeable decrease in the severity and frequency of infections once a child was started on gamma globulin, however, gamma globulin blood levels taken either before or during treatment had no prognostic value regarding the effectiveness of therapy. Gamma globulin blood levels determined during an acute asthmatic episode were normal. Hyposensitization therapy where indicated was never supplanted by gamma globulin therapy. Those children whose allergic conditions were aggravated by frequent infections did much better when on combined hyposensitization therapy and gamma globulin. In view of the expense of gamma globulin it is suggested that the smaller dosage of 0.15 c.c. per pound of body weight be tried first before increasing the amount to 0.2 c.c. per pound of body weight. R. W.

DERMATOLOGY

Schönlein-Henoch Syndrome—Anaphylactoid Purpura. Blattner, R.: J. Pediat. **57**: 137, 1960.

It is now generally accepted that Schönlein-Henoch purpura (anaphylactoid purpura) is a hypersensitivity reaction. The condition may occur in young infants, but is generally seen in children between 3 and 7 years of age. The primary reaction is believed to be an acute inflammatory exudate containing polymorphonuclear cells and round cells which surrounds the small blood vessels of the corium. Eosinophils may be present and as a rule the erythrocyte count varies with the severity of the purpura. Characteristically the capillaries are involved but pathologic changes in precapillary arterioles and a necrotizing arteriolitis with fibrin thrombi have been described. Similar lesions have been induced experimentally in animals injected with antibodies which had been produced against the endothelial cells lining the arteries.

The syndrome is not considered to be familial but, in some instances, a family history of allergy is present, and there have been a few reports of the condition occurring in siblings. Renal symptoms are well recognized as part

of anaphylactoid purpura. Recently renal biopsy studies of patients with the syndrome have demonstrated definite glomerular lesions. Although potentially serious, the prognosis of the kidney disorder in anaphylactoid purpura may not be unfavorable. H. F.

Skin Histamine Levels in Chronic Atopic Dermatitis. Johnson, H. H., Jr., DeOreo, G. A., Lascheid, W. P., and Mitchell, F.: J. Invest. Dermat. **34**: 237, 1960.

Histamine determinations were made on skin biopsy specimens obtained from the involved antecubital area of 16 adults with chronic atopic dermatitis and from the same region of 15 normal adults. The eczematous patients had not received steroids or x-ray therapy for at least 1 month. The histamine content of the normal skin specimens varied from 4.2 to 14.3 mcg. of base per gram of skin with an average of 9.2 mcg. per gram. The eczematous skin specimens contained between 9.7 and 24.8 mcg. of histamine base per gram with an average of 16 mcg. per gram. Although the difference in the histamine content of the two groups was considered significant, the results of this study did not warrant any conclusion concerning the role of histamine in atopic dermatitis. B. S.

ANAPHYLAXIS

Anaphylactogenic Properties of Soluble Antigen-Antibody Complexes in the Guinea Pig and Rabbit. Weigle, W. O., Cochrange, C. G., and Dixon, F. J.: J. Immunol. **85**: 469, 1960.

In these experiments, anaphylactic reactions were produced in guinea pigs and rabbits by the intravenous injection of soluble antigen-antibody complexes. In the guinea pig, classical symptoms of anaphylaxis were produced which could be inhibited with antihistamines. When I^{131} labeled bovine serum albumin complexes were injected there was a preferential localization of I^{131} activity in the lungs during anaphylaxis. A similar localization of I^{131} activity was observed in the lungs of guinea pigs passively sensitized with I^{131} anti-BSA and challenged 2 days later with BSA. The localization was greater in fatal anaphylaxis than in mild sensitivity reactions.

In rabbits the injection of large amounts of soluble complexes also produced typical anaphylactic reactions. They occurred in the absence of obvious embolization of the pulmonary circulation, suggesting that other mechanisms, such as vasoconstriction of pulmonary arteries by a humoral factor released secondary to antigen-antibody interaction, may also play an important role in rabbit anaphylaxis. H. Pelz

MISCELLANEOUS ALLERGIES

Anaphylactic Reaction to ACTH. Zucker, A., and Bendo, D.: New York J. Med. **61**: 623, 1961.

An acute allergic reaction after the intravenous injection of ACTH in a 50-year-old male asthmatic, with a history of asthma of 2 to 3 years' duration, was observed. He had mild emphysema and showed positive skin reactions to ragweed, feathers, house dust, molds, and pork. Immunization therapy afforded only temporary relief and it was necessary on several occasions to hospitalize him for courses of steroid and ACTH therapy. During one of his previous hospitalizations, he had been given an infusion of 1,000 c.c. of 5 per cent glucose in water to which aminophylline and 20 units of ACTH had been

added. While he was receiving the fluid he developed generalized urticaria and increasing dyspnea. ACTH was suspected as the cause. The infusion was stopped immediately and he responded promptly to emergency measures. Six months later after another bout of severe protracted asthma the patient was again hospitalized. The house physician unaware of the previous episode ordered an intravenous infusion containing aminophylline and 40 units of aqueous ACTH. Ten minutes after the infusion had been started the patient became cold, clammy, intensely cyanotic, and stopped breathing. Blood pressure and pulse were both unobtainable. He was immediately given 1 c.c. of epinephrine intravenously and artificial respiration was instituted. Oxygen was administered by intermittent positive pressure and 100 mg. of hydrocortisone was injected intravenously. The vital signs quickly reappeared and within a few hours he was comfortable. A scratch test performed with a 1:100 dilution of ACTH resulted in a strong positive reaction. An intracutaneous test with a 1:10,000 dilution of aqueous ACTH produced such a large wheal and erythema that it was necessary to place a tourniquet on the arm and give the patient an injection of epinephrine to stop the reaction. Passive transfer tests were positive with both pork and ACTH in a dilution of 1:100. The authors suggest that patients who are to receive intravenous ACTH therapy should be carefully questioned to determine possible sensitivity to ACTH or pork. R. W.

Respiratory Allergy in Patients With Cystic Fibrosis. Kulczycki, L. K., Mueller, H., and Shwachman, H.: J. A. M. A. **175**: 358, 1961.

Cystic fibrosis (mucoviscidosis) is a generalized disease of the mucous-secreting (exocrine) glands, most often affecting children but, not infrequently, found in adults. The lungs, liver, and pancreas are the sites of the major pathologic lesions in the disease. In patients with pulmonary disease, signs and symptoms of involvement may be suggestive of an allergic respiratory disorder.

In the present study 266 patients with cystic fibrosis, ranging in age from 1½ years to 35 years, were seen during an 18-month period. Their disease status was evaluated on the basis of history, physical examination, and clinical and laboratory studies which included quantitative sweat electrolyte studies, duodenal fluid assays, x-rays and, when indicated, allergy skin testing. Thirty-seven per cent of the 266 patients had a history of recurrent wheezing, cough, and dyspnea; 62 per cent had a family history for allergy; and definite clinical allergy was confirmed in 17.7 per cent, 44 or 16.6 per cent of whom had respiratory allergy. Thirty-two of these were males. Nasal polyposis was present in 15 patients in the series, but in only 7 of these could allergic disease be demonstrated.

The sweat electrolyte levels of all these patients, atopic or nonatopic, showed a high concentration of sodium and chloride. Patients in a noncystic fibrosis allergic control group all had normal levels. Although there are many etiologic, clinical, and pathologic differences between asthma and cystic fibrosis, there are many similarities in the pulmonary manifestations of the two conditions which may coexist in the same patient. Because of the close resemblance in response of the mucous membrane of the upper respiratory tract in the two conditions, cystic fibrosis may be easily overlooked unless sweat electrolyte studies are performed. H. F.

Anaphylactic Reaction to Chymotrypsin. Howell, I. L.: J. A. M. A. **175**: 322, 1961.

An intramuscular injection of chymotrypsin given to a 25-year-old male was followed within 5 to 10 minutes by collapse and unconsciousness with

indiscernible pulse or respirations. This patient had had at least one previous injection of chymotrypsin 3 years prior to the present incident. Epinephrine 1:1000, 1 ml. administered first subcutaneously and then 1 ml. intracardially, restored the pulse beat and stimulated respiration. The patient was removed to a hospital where in spite of additional symptomatic and supportive measures he remained comatose for 4 hours. No neurologic signs were apparent until the fifth day after the onset of symptoms, when the patient manifested increasingly severe signs of cerebral involvement, which were attributed to anoxia. These signs cleared slowly over the next several months. H. F.

The Incidence of Reactions Following the Oral Administration of Phenethicillin. Frank, L., Katz, S., and Plotz, C.: New York J. Med. **61**: 593, 1961.

The authors treated 652 patients with 250 mg. of phenethicillin (Maxipen) 4 times daily for an average period of 7 days. A history of previous allergic reactions to parenterally administered penicillin was obtained from 12 of the patients. Eight patients (1.2 per cent) of the entire group developed allergic reactions following the biosynthetic penicillin therapy. Two of these had a past history of known parenteral penicillin sensitivity. One of the patients had a severe, erythematous, urticarial reaction which began 1 day after the administration of phenethicillin and persisted for many weeks even though the drug had been discontinued. Four mild cases of urticaria were observed and 2 additional patients had mild reactions which were like those of serum sickness. Three patients who were having cutaneous reactions from biosynthetic parenteral penicillin had their symptoms clear up while continuing on oral phenethicillin. The incidence of reactions with oral phenethicillin was comparable to that encountered with oral crystalline penicillin G and was significantly lower than the reaction rate observed with parenteral penicillin therapy. R. W.

Transfer of Delayed Hypersensitivity to Coccidioidin in Man. Rapaport, F. T., Lawrence, H. S., Millar, J. W., Pappagianis, D., and Smith, C. E.: J. Immunol. **84**: 358, 1960.

The authors investigated the mechanisms by which the transfer factor in extracts of human leukocytes sensitized to coccidioidin induced generalized delayed sensitivity in nonsensitive recipients. The leukocytes obtained from coccidioidin-sensitive residents of an area endemic for *Coccidioides immitis* were DNase-treated and administered to individuals who were lifelong residents of an area free of the organism. Delayed reactivity was transferred in 28 out of 35 attempts. As with bacterial delayed hypersensitivity enhancement of the induced sensitivity in the recipient could be accomplished by injecting coccidioidin antigen into the transfer site or by incubating leukocytic extract with antigen prior to injection. Attempts to transfer sensitivity with leukocytes obtained from a negative donor were unsuccessful in 8 out of 9 consecutive trials. There is no explanation for the single exception. Transferred sensitivity to coccidioidin was shown to persist as long as 15 months. H. Pelz

The Immunologic Properties of Coccidioidin as a Skin Test Reagent in Man. Rapaport, F. T., Lawrence, H. S., Millar, J. W., Pappagianis, D., and Smith, C. E.: J. Immunol. **84**: 368, 1960.

It was found in this study of delayed-type sensitivity that the behavior of coccidioidin in nonsensitive and specifically sensitive individuals is very similar to that described for tuberculin in its specific allergic states. Repeated

intradermal testing of negative reactors with coccidioidin at weekly intervals for two, three, and four successive times did not induce delayed sensitivity. High concentrations of coccidioidin (1:10 and undiluted) were used for these tests instead of more dilute solutions previously employed. Repeated intradermal coccidioidin testing with these dilutions elicited stronger or anamnestic responses in subjects with weak or latent sensitivity response. There was no constant relationship between the level of cutaneous reactivity to coccidioidin and the presence or titer of complement-fixing serum antibody. Each of 20 individuals studied in the endemic area had either clinical or immunologic evidence of past coccidioidal infection reaffirming the extremely high infectivity of *C. immitis*. H. Pelz

Guillain-Barré Syndrome Resulting From Tetanus Antitoxin Injection. Miglets, A. W., Bartlett, G. W., Arbesman, C. A., and Loeser, W. D.: Neurology **10**: 658, 1960.

A case of Guillain-Barré syndrome (polyradiculoneuritis with albuminocytologic dissociation) is reported occurring in a 37-year-old woman following an injection of 0.5 ml. of undiluted tetanus antitoxin. A preliminary skin test with the antitoxin had produced only an erythema. The patient had received a previous injection of tetanus antitoxin at the age of 6. She gave a history of having developed a rash after a penicillin injection, and she stated that she was allergic to pork. Seven days after the injection of the antitoxin, she developed chills, fever, and joint pains. In the next few days she complained of headache, backache, and exhibited a left facial palsy, lower and upper extremity weakness, and loss of position sense in the toes of both feet. The spinal fluid showed marked albuminocytologic dissociation. Gradual improvement followed so that by the third week after injection she showed some return of leg power and arm strength and some improvement in spinal fluid findings. After one year, complete muscle power had returned except for some residual weakness in the deltoids and triceps. Serum obtained on hospital day 156 revealed hemagglutinins to horse serum in a titer of 1:32,000 (tanned rbc method) and at day 222 a titer of 1:12,000. The presence of precipitins, anaphylactic or Prausnitz-Kustner antibodies could not be demonstrated. The serologic findings suggest that an hyperimmune response to horse serum may be one of the mechanisms responsible for this syndrome. H. Pelz

IMMUNOLOGY

Experimental Hypersensitivity in the Rabbit: Potentiating Effect of Prior Sensitization on Renal Lesions Produced by Bovine Gamma Globulin. West, C. D., Hinkle, N. H., and Landing, B. H.: J. Lab. & Clin. Med. **55**: 439, 1960.

Rabbits were sensitized to bovine gamma globulin (BGG) either with the antigen mixed with Freund's adjuvant and injected subcutaneously at 5 sites or as alum-precipitated BGG injected intravenously daily for 8 days. Renal status was followed by tests of serial blood and urine specimens for urea and protein. Proteinuria of 3 or more days' duration occurred in only 7 per cent of nonsensitized animals, whereas in animals sensitized by adjuvant the incidence was 80 per cent, and in those sensitized by alum-precipitated BGG, 47 per cent.

In sensitized animals, urine protein concentrations reached levels as high as 6.5 Gm. per cent. The proteinuria averaged 5 days in duration. Microscopic hematuria was found in 50 per cent of the specimens tested. The BUN

rose above 27 mg. per cent in 63 per cent of the animals tested. This elevation usually lasted 1 or 2 days. There was no correlation between hematuria, proteinuria, and azotemia.

In nonsensitized animals, three phases of antigen disappearance could be distinguished. The first, an equilibrium phase, lasted 48 hours, the catabolic phase from 2 to 4 days, and the third, or immune phase, in which rapid removal of antigen occurred by combination with newly formed antibody continued to the eleventh day. The half-life of BGG was 2.35 days. In the sensitized animals, no catabolic phase could be distinguished; the pre-existing immunity accelerated the rate of fall and there was complete disappearance of the antigen 5 days earlier than in nonsensitized animals. In correlating the development of the nephritis by the appearance of the proteinuria with the disappearance of the antigen, it was calculated that the circulating BGG level was less than 0.15 mg. per milliliter at the time of onset of the nephritis.

No lesions were seen in animals killed 1 or 2 days before the expected onset of proteinuria. In those sacrificed on the first day of proteinuria, there was edema and proliferation of the glomeruli with obliteration of the capillary loops and thickening of all structures. Glomeruli located in the corticomedullary junction showed encapsulated hemorrhage, the result of focal necrosis of capillaries. Three to 5 days after the appearance of proteinuria, the glomeruli had shrunk and there was an increase in nuclear density. The capsular space was now large and, in some cases, contained inspissated protein. The interstices of the cortex were infiltrated with plasma cells and lymphocytes in a patchy distribution. In animals killed after the disappearance of proteinuria, the glomeruli were normal, except for those in which encapsulated hemorrhage had occurred. These, which were located at the corticomedullary junction, showed a large capsule which appeared either to be empty or to contain a small nubbin of glomerular tissue.

In other organs, pathologic changes were also observed, but not with the frequency or severity of nephritis. Most striking was the complete absence of polyarteritis, a lesion seen often after injection of BSA. E. W.

Immunologic Studies of Heart Tissue. III. Occurrence of Bound Gamma Globulin in Auricular Appendages From Rheumatic Hearts: Relationship of Certain Histopathologic Features of Rheumatic Heart Disease. Kaplan, M. H., and Dallenbach, F. D.: J. Exper. Med. **113**: 1, 1961.

Deposition of bound gamma globulin was demonstrated in the auricular appendages of a significant number of patients with rheumatic heart disease by the fluorescent antibody technique. These deposits were irregularly distributed in the myocardium, occurred independent of Aschoff bodies, were found mainly in the myofibrils and, to a lesser degree, in connective tissue and blood vessel walls.

Quick frozen sections of atrial appendages removed at operation from 100 patients with inactive rheumatic heart disease were stained with fluorescein-labeled rabbit antihuman-globulin, -fibrin, and -albumin antibodies, respectively. Companion pieces fixed in formalin were stained with conventional stains. Thirty-three similarly treated control specimens were obtained from hearts of patients with diseases other than rheumatic fever or of normal individuals.

Eighteen of the 100 atria from patients with rheumatic heart disease manifested significant deposition of bound gamma globulin, 12 others showed lesser deposits and the remaining 70 specimens showed no deposition. Thirty-two of the 33 control specimens revealed no gamma globulin deposition. The gamma globulin was noted to occur mainly within the myofibrils involving the sarcolemma. Occasionally connective tissue bundles, blood vessel walls,

epi- and endocardium exhibited focal deposition of gamma globulin. By the use of the conventional stains, eosinophilic masses of fibrinoid material were demonstrated within sarcolemma. These fibrinoid masses corresponded to the deposits of fluorescein-stained, bound gamma globulin. Fluorescein-labeled antifibrin and albumin antibody demonstrated these substances to be deposited in normal as well as in rheumatic hearts and, in the latter specimens, occurred independent of globulin deposits. Inflammatory reaction was not observed around the fibrinoid deposition, and there was no correlation between the presence of bound gamma globulin and Aschoff bodies. Fluorescence was not observed in any of the components of the Aschoff body.

These data are consistent with the concept that altered tissue per se, and not deposition of fibrin, causes tissue eosinophilia within fibrinoid deposits, and that this tissue alteration is usually associated with gamma globulin deposition. The presence of bound gamma globulin in the form of fibrinoid may be regarded from two points of view. The first viewpoint is that the deposits are due to an antigen-antibody reaction. The second viewpoint is that this deposition is a nonimmunologic reaction, i.e., fibrinoid deposition due to tissue response characteristic of rheumatic fever or to tissue reactivity of complement-like, abnormal globulins present in this disease.

D. Stein

Toxic and Allergic Properties of Pollen Extracts in the Mouse. Kind, L. S., and Roesner, L.: J. Immunol. **84**: 390, 1960.

Recent reports have called attention to the similarity of endotoxin-like reactions and hypersensitive responses to pollens in mice. The authors have studied the production of allergic reactions to pollens in pertussis-inoculated mice. The intravenous injection of water-soluble extracts of rye grass, Bermuda grass, timothy, and ragweed killed 64 per cent of 87 mice which had been vaccinated with pertussis vaccine 5 days previously. Only 2 per cent of unvaccinated controls died. Death occurred usually in from 2 to 8 hours following prostration, weakness, hypothermia and immobilization. Cortisone was protective. Anaphylaxis was readily induced in the mouse with grass pollen extract but needed the aid of pertussis vaccine in ragweed sensitization. It is suggested that as a result of such studies methods may now be available in this laboratory animal for studying and separating the toxic and allergic properties of pollen extract.

H. Pelz

Studies on the Transfer of Antibody Formation by Iso- and Heterotransplants. Chin, P. H., and Silverman, M. S.: J. Immunol. **85**: 120, 1960.

The authors studied the production of circulating antibody in lethally irradiated recipient mice following transplantation of spleen and bone marrow cells obtained from rats immunized to *Salmonella typhosa*. Antibody production following transfer of spleen cells from immunized mice into normal and irradiated isologous recipients was also investigated. Continued synthesis of antibodies by the transplanted tissues was achieved with both heterologous and isologous spleen transfers. Identification of rat gamma globulin was accomplished by use of the Ouchterlony double diffusion agar test, coupled with a modified Coombs test.

In contrast to these findings, circulating agglutinins against *Sal. typhosa* could not be demonstrated following transfer of isologous or heterologous bone marrow, even though the source of the tissue was the same as the spleen cells used in this experiment. No demonstrable antibody response occurred even after restimulation of transplanted marrow cells with antigen. These failures may be attributed to the dearth of immunologically competent cells in the marrow when compared to the predominance of lymphoid cells in the

spleen. Hence it is recommended that "findings following transplantation of lymphoid tissue should not be directly extrapolated to interpret observations obtained from bone marrow transplantation." H. Pelz

Studies on Trichophytin Sensitivity. Cruickshank, S. N. D., Trotter, M. D., and Wood, S. R.: J. Invest. Dermat. **35**: 219, 1960.

One group of guinea pigs was sensitized by subcutaneous injection of acetone dried mycelium of Trichophyton mentagrophytes suspended in Freund's adjuvant. A second group was infected with the viable mycelium by scarification on the shaven flanks. Within 7 days the latter group developed clinical and histologic evidence of an active infection which reached its height in 14 days and subsided after another week. After an interval of one month, the infected animals were given another inoculation of live mycelium. The resultant lesions were more violent than those following the initial inoculation and appeared almost immediately. The height of the reaction was reached on the fifth day and the lesions regressed by the fourteenth day. Sensitized animals inoculated with living mycelium followed a course of infection similar to that of the re-infected animals. Thus, both groups demonstrated the Koch phenomenon.

When trichophytin was injected intracutaneously into infected and sensitized animals, an immediate reaction was barely detectable. However, when these animals were previously injected intravenously with Evan's blue dye, a distinct blueing of the test area was noted in about 10 minutes. Anaphylaxis was induced in 3 animals of each group by the intracardiac injection of purified trichophytin. Passive cutaneous anaphylaxis was demonstrated with sera from 2 infected and 2 sensitized animals. Negative reactions were obtained with serum from a normal animal.

Delayed reactions to intracutaneously injected trichophytin in sensitized guinea pigs usually appeared at about 6 hours and became maximal at 24 hours. By testing with 4 concentrations of trichophytin it was found that the mean diameters of the delayed reactions at 24 hours were proportional to the logarithms of the concentrations of the trichophytin. This relationship was used as a basis for assay of commercial trichophytins.

Normal guinea pigs were injected intraperitoneally with washed peritoneal cells from either sensitized or normal animals. The intracutaneous injection of trichophytin 4 days later produced positive delayed reactions in those animals which had received the sensitized cells. Delayed reactions could be demonstrated in the passively sensitized animals as long as 22 days later. Negative reactions occurred in the animals which had received normal cells.

A method of preparation of a purified trichophytin from ethylene glycol extracts of acetone dried powdered mycelium is described. The active antigen or antigens are essentially polysaccharides with a small amount of firmly bound protein or peptide. Preliminary comparative intracutaneous tests of this purified trichophytin with commercial preparations in human beings showed that the purified material produced fewer immediate and delayed reactions. Whether this finding is due to a loss of nonspecific irritants or specific antigens in the purified product remains to be determined. B. S.

The Effect of Antigen Concentration on the Initiation of Detectable Antibody Synthesis in Rabbits. Farr, R. S., and Dixon, F. J., Jr.: J. Immunol. **85**: 250, 1960.

In rabbits the concentration rather than the total dose of antigen appeared to be the critical factor in eliciting an antibody response to the injection of small amounts of bovine serum albumin in water-in-oil emulsion.

Studies were carried out on rabbits using soluble protein antigens and employing elimination of I^{131} labeled antigen from circulation, the precipitation of soluble I^{131} labeled antigen-globulin complexes by ammonium sulfate, precipitin tests, and the ability of the initial injection of antigen to prepare an animal for an anamnestic response, as items in a test system for antibody determination. With the concentration of antigen in the aqueous phase of the adjuvant remaining constant, it was possible to reduce the total amount of antigen given by a factor of 10 without affecting the proportion of animals that responded with antibody synthesis. With the total amount of injected antigen remaining constant, it was possible to decrease the percentage of animals responding with detectable antibody synthesis by employing larger volumes of adjuvant and lower concentrations of antigen in the aqueous phase. The minimal amount of BSA required to initiate synthesis of detectable amounts of antibody was approximately 6 μg when given intravenously and 1:100 of this amount or 0.05—0.1 μg when given as a water-in-oil emulsion. One of the advantages of water-in-oil emulsion adjuvant appears to be that the small amounts of antigen are maintained in the host at their original concentration until liberated from the oil continuum. The fact that the concentration of the antigen seems to be a determining factor in this process seems to imply that the initial antibody synthesis took place at a lymphoid site close to the inoculum. H. Pelz

Studies of Arthritis and Other Lesions Induced in Rats by Injection of Mycobacterial Adjuvant. II. Evidence That the Disease is a Disseminated Immunologic Response to Exogenous Antigen. Waksman, B. H., Pearson, C. M., and Sharp, J. T.: J. Immunol. **85**: 403, 1960.

Following the intradermal, subcutaneous, or footpad inoculation of heat-killed tubercule bacilli in mineral oil into rats, a disseminated inflammatory disease involving many organ systems resulted. Rat litters differed in their susceptibility and animals less than 5 weeks of age appeared to be resistant. Rats, in whom the disease was induced, revealed a delayed-type skin reactivity to tuberculin and the parenteral use of tuberculin in these sensitized animals caused a transient flare-up of the disease process. An anamnestic response could be achieved in the subsiding phase of the disease process. In rats receiving tubercle bacilli in oil intradermally, irradiation of 600 r suppressed the appearance of this syndrome. Exposure of animals to single or repeated subcutaneous injections of tubercle bacilli during the first 3 weeks of life inhibited their subsequent capacity to develop the disseminated connective tissue lesions but did not prevent subsequent susceptibility to induced allergic encephalomyelitis. The induction of inflammatory responses in many organ systems was effected with transfer of sensitized lymph node cells in normal, irradiated, and tolerant recipients. Trauma or previous nonspecific inflammation predisposed localization of the disease process to the involved area. It was concluded that the lesions produced represented a delayed hypersensitive response to the widespread dissemination of antigenic constituents, probably derived from the injected tubercle bacilli. H. Pelz

Immunologic Reactions in Psoriasis. Aswaq, M., Farber, E. M., Moreci, A. P., and Raffel, S.: A. M. A. Arch. Dermat. **82**: 663, 1960.

The possibility that an autoimmune reaction might be the mechanism in the causation of psoriasis was investigated in guinea pigs by the passive cutaneous technique. The animals were injected intradermally in from 2 to 6 different sites with sera obtained from 32 patients with psoriasis, 10 with atopic dermatitis, and 9 normal controls. Homogenates of the psoriatic lesions

were prepared from punch biopsy specimens. Homogenates were also prepared from uninvolved skin adjacent to the active plaques. The diluted homogenate suspensions were mixed with a small quantity of Evans blue dye and injected intravenously into guinea pigs 6 to 18 hours after skin sensitization with the sera. Sites sensitized with 26 (81 per cent) of the 32 psoriatic sera yielded positive reactions after intravenous injection of psoriatic plaque homogenate. The typical reactions which were unlike the rapidly appearing evanescent reactions of passive cutaneous anaphylaxis began 4 to 5 hours after intravenous injection and were manifested by edema, induration, and minimal erythema. Localization of the dye occurred slowly and to a moderate degree and the complete reaction persisted for approximately 48 hours. Sites injected with either atopic or control sera in the same animals were negative. Of 10 psoriatic sera which were also challenged with homogenates prepared from normal appearing skin adjacent to psoriatic lesions, 4 positive reactions of mild degree were observed. Psoriatic sera did not sensitize guinea pig skin to normal skin homogenates. Skin sites injected with normal serum or atopic serum failed to react to intravenous challenge with psoriatic plaque homogenates. The authors believe that these studies suggest the possibility that an autoimmune mechanism may play a role in the production of psoriasis.

R. W.

The Antibody Molecule in Chronic Nonspecific Thyroiditis: Electrophoretic Patterns of Serum. Shulman, S., Rose, N. R., and Witebsky, E.: J. Lab. & Clin. Med. **55**: 733, 1960.

Electrophoretic studies were made on the sera of 37 patients with the clinical diagnosis of thyroiditis. All of these samples had been shown to have circulating antibodies to human thyroid extract. Although only 10 sera had precipitins, all of them showed positive results by tanned cell hemagglutination. When these sera were examined by filter paper electrophoresis, it was found that only 27 per cent of the samples could be considered to have an elevated gamma globulin. Forty-six per cent of the sera showed an increase in alpha globulin, but none of these elevations was very high. Lesser, but apparently significant, increases in beta and $alpha_1$ globulin levels were also found.

The sera of 14 patients with struma lymphomatosa or Hashimoto's disease who were persistently negative when tested for autoantibodies showed elevated gamma globulin levels in 57 per cent and 36 per cent of the sera, respectively. In contrast, none of the sera showed an increase in the beta or $alpha_1$ globulin or a decrease in albumin.

Three sera from patients with chronic thyroiditis were fractionated by means of continuous flow paper electrophoresis. In 2 of these cases, there was an increase in the $alpha_2$ globulin, and, in 1, in the $gamma_1$ globulin. In the sera of these patients, the antibody, as judged by the tanned cell hemagglutination technique, was identified as $gamma_2$ globulin. E. W.

Effects of X-rays on Antibodies. Luzzio, A. J.: J. Infect. Dis. **106**: 87, 1960.

Previous studies have demonstrated that exposure to x-rays can selectively influence human red blood cell agglutinin titers. These findings suggest that immune serums can be prepared by inactivating unwanted active sites in such serums.

The agglutinin titers of serum to several strains of Salmonella and Proteus serums were determined before, and subsequent to, exposure to various doses of x-ray. Results indicated that agglutinins for these bacterial antigens

demonstrated different radiosensitivities when exposed to the same dose levels of x-ray. These variations in sensitivity were such as to suggest an orderly radioinactivation of antibody molecules in serums containing more than one immunological specificity.

These findings are in accord with the selective results obtained with irradiation of red blood cell agglutinins and suggest that various antibody combining sites possess specific radiosensitivities and that antibodies may be removed selectively from polyvalent serum by x-ray. H. F.

6-Mercaptopurine in Immunologic Responsiveness. Robinson, J. L., and Christian, C. L.: Nature **187**: 796, 1960.

The intramuscular injection of 6-mercaptopurine failed to completely suppress antibody formation when ovalbumin antigen was incorporated in complete Freund's adjuvant. Precipitating antibodies were not detectable, nor was passive cutaneous anaphylaxis demonstrable in serums drawn up to 14 days after sensitization, however, both types of reactions could be demonstrated in 21 day serums. Homografts were rejected in all animals living beyond 21 days but autografts were universally successful. H. F.

PHARMACOLOGY, PHYSIOLOGY, AND PATHOLOGY

Testing of the Permeability Increasing Activity of Human Serum Preparations in the Guinea Pig and in Man. Moller, H., and Rorsman, H.: J. Invest. Dermat. **35**: 235, 1960.

Ten patients with venereal or skin diseases were injected intracutaneously on uninvolved skin of the back with 0.1 ml. of autologous serum in twofold serial saline dilutions from 1:32 to 1:2048. Sodium fluorescein was injected intravenously immediately thereafter and within 3 minutes the responses at the skin sites were read under Wood's light. The highest serum dilution eliciting a positive response was considered as the end point. Antihistamines and steroids were discontinued for 24 hours prior to the tests. The 10 human sera in similar dilutions were then injected intracutaneously into guinea pig skin in 0.1 ml. volumes. Just prior to the tests each animal received Pontamine sky blue 6x dye intravenously. The highest serum dilution producing a bright blue area of 5 mm. or more in diameter was considered as the end point. A close correlation was found between the highest dilution of each serum which caused increased permeability of the skin in human beings and in guinea pigs.

Ten guinea pigs were then tested in a similar manner with dilutions of human albumin, alpha globulin, beta globulin and gamma globulin, each in an impure form. The alpha and beta globulins showed the greatest permeability increasing activity. B. S.

Isoproterenol Vasomotor Reversal by Sympathomimetic Amines. Walz, D. T., Kappaniye, T., and Maengwyn-Davies, G. D.: J. Pharmacol. & Exper. Therap. **129**: 200, 1960.

Isoproterenol (Isuprel) ordinarily lowers blood pressure. Intravenous infusion of anesthetized, atropinized cats and dogs with a variety of sympathomimetic amines, including ephedrine, Propadrine, phenylephrine (Neo-Synephrine), and Tuamine reversed this effect so that intravenous injection of isoproterenol during or after the infusion of these drugs raised blood pressure. The usual vasopressor response to epinephrine was variously affected by sympathomimetic amines. When isoproterenol infusion itself was supplemented or followed by challenging isoproterenol injection, blood pressure

rose; this reversal of effect lasted up to 8 hours after the infusion was discontinued. Tyramine did not reverse the pressor response to isoproterenol and only a slight reversal was seen with epinephrine. Dibenamine administration after induction of reversal to isoproterenol re-established the vasodepressor response to isoproterenol. The sympathetic blocking agent DCI blocked the depressor effect caused by isoproterenol but did not cause this drug to raise blood pressure. Animals pre-treated with DCI and infused with phenylephrine still responded with increased blood pressure to challenging doses of isoproterenol (reverse effect). "Hence, it is concluded that, besides possible blockade of inhibitory receptors by the large amounts of the sympathomimetic amines employed, a sensitization of the excitatory effector site must take place." E. K.

OTORHINOLOGY AND OPHTHALMOLOGY

Epistaxis in Allergic Children. Scott, R. B., and Epps, R. P.: Ann. Allergy **18**: 728, 1960.

Four hundred and fifty children seen in private practice and in a hospital out-patient department were classified as "allergic" if they had exhibited allergic reactions, "potentially allergic" if the family history of allergy was positive, and normal where these conditions were not met. Fifty additional private patients with epistaxis and allergy were also surveyed. A history of epistaxis was obtained in 18.51 per cent of the 189 normals, in 24 per cent of the 78 "potentially allergic," and in 26 per cent of the 183 allergic individuals. Epistaxis was equally as common in males as females, tended to appear later than the time of onset of allergic reaction, and in some cases lead to anemia. It was concluded that epistaxis should be added to the manifestations of nasal or paranasal allergy in children. E. K.

MISCELLANEOUS

The Value of Corticosteroids (Corticoids) in Allergic Diseases. Tuft, L.: J. A. M. A. **174**: 1801, 1960.

Although experience has led to a more liberal approach in the use of corticosteroids in allergic disease there still exists considerable difference of opinion regarding the clinical use of these medications. The author believes that they have a definite place in the treatment of the reversible type of allergic diseases, particularly when conventional therapy has failed. Their short-term use is advisable in the acute or subacute allergies such as status asthmaticus, drug and serum reactions, severe acute urticaria and angioedema, and acute allergic dermatosis. Chronic intractable asthma is often an indication for their long-term use, but only after failure of the patient to respond to conventional therapy. Corticosteroids are of little value in the treatment of allergic rhinitis, hay fever, and chronic urticaria. Nasal polypi can be shrunken or made to disappear by the local injection of the corticoids. Their use is definitely indicated in the collagen diseases where they may help to prolong life, although they have no effect on the ultimate outcome of the disease.

ACTH by intravenous injection may be employed in patients with status asthmaticus or in acute urticaria or angioedema. It is also of value in the treatment of certain acute cases of contact dermatitis, atopic eczema, and in the severe delayed type of serum or drug reactions. Although patients on

long-term corticoid therapy may be given ACTH to stimulate the adrenal cortex, this is rarely necessary since low maintenance doses do not appear to suppress the adrenals to a noticeable degree.

Changes and substitutions in the structural formulae of the corticoids have resulted in compounds with more powerful therapeutic activity and less side effects. Best results with steroids are obtained by administering large doses at the onset and maintaining adequate dosage until the maximal therapeutic effect is obtained. Thereafter, gradual reduction in dosage may be instituted. All patients on corticoid therapy, especially those with intractable asthma, should continue to take bronchodilators and expectorants or antihistaminics in the case of nasal allergy. Hyposensitization therapy and dietary control should also be continued. Patients occasionally develop a corticoid "habit" or "addiction" and therefore should be informed of the possible dangers from the indiscriminate use of these medications. In general it can be stated that serious side effects can be avoided by properly controlled dosage and the use of concomitant conventional therapy. H. F.

Soybean Goiter: Report of Three Cases. Shepard, T. H., Pyne, G. E., Kirschvink, J. F., and McLean, M.: New England J. Med. **262**: 1099, 1960.

Three children developed goiters while on soybean milk formulae. In the first patient, the thyroid became enlarged when she was placed on soybean formula at 3 months of age. A biopsy at 10 months revealed hyperplastic thyroid tissue consisting of pale-staining tall columnar cells in folds, minimal numbers of acini, and only small amounts of colloid. In the second case, soybean was given at birth and a goiter was soon noted. The gland which was symmetrically enlarged at 3 months of age could no longer be felt after 6 weeks of cow's milk. In the third patient, soybean milk had been started at the age of 3 months and a goiter was noted on examination 3 years later. Iodides were added to the diet, and after 15 days the goiter could not be felt.

The three patients were euthyroid as judged by physical findings and normal growth. Serum protein-bound iodine values were slightly low. Serum cholesterols were normal. In 2 cases there was a marked increase over normal of I^{131} uptake in 24 hours while the patients were on soybean formula. In the other case a marked increase in the I^{131} uptake occurred at 4 hours and returned to a high normal value at 24 hours. After discontinuing soybean in the first 2 patients, the I^{131} uptakes became normal. Case 3 was kept on soybean while iodine was added to the diet and the I^{131} uptake returned to normal. The histologic picture of the thyroid gland was similar to the hyperplasia observed in thyroid glands early in iodine deficiency. Evidence indicates that the mechanism of soybean goiter may be due to iodine deficiency. M. C.

Agranulocytosis and Sepsis Associated With Prednisone. Rokseth, R.: Lancet **1**: 680, 1960.

A 65-year-old woman was treated with prednisone for relief of erythema multiforme. After taking 5 to 15 mg. daily for 4 weeks the condition completely subsided but the patient continued to take the medication. Six weeks after the institution of prednisone therapy she developed urticaria, a sore throat, and general malaise. Prednisone was discontinued and the urticaria subsided immediately but her condition rapidly deteriorated and she was hospitalized. She looked pale, had a purulent stomatitis, and a blood count showed 9 grams of hemoglobin, 500 white cells per cubic millimeter, and an

absence of polymorphonuclear cells on the blood smear. Bone marrow aspiration revealed a maturation arrest at the promyelocyte stage. A profuse growth of pyogenic staphylococci was obtained on blood culture. She was treated with erythromycin and blood transfusions and made an uneventful recovery during the next 7 to 14 days. Scratch tests performed with prednisone were negative. There was absolutely no history of any other drug ingestion besides the prednisone. Continued follow-up of the patient during the next 2 years failed to reveal any additional underlying mechanism which might have caused the agranulocytosis besides the ingestion of prednisone. R. W.

Agranulocytosis Due to Chlordiazepoxide Hydrochloride. Kaelbling, R., and Conrad, F. G.: J. A. M. A. **174**: 171, 1960.

Chlordiazepoxide (Librium) like many other drugs containing benzene-ring structures can cause agranulocytosis. A 23-year-old psychiatric patient who had on two occasions developed skin reactions after the use of chlorpromazine hydrochloride was started on treatment with chlordiazepoxide. Three days later she developed a sore throat and generalized fatigue and a temperature of 102° F. A blood count revealed a marked granulocytopenia. The drug was promptly discontinued and treatment with prednisone, folic acid, and penicillin was instituted. The patient made an uneventful recovery. In retrospect, the authors believe that the previous reactions to chlorpromazine should have been a warning of the possibility of reactions to other drugs. They believe that weekly blood counts should be done on all patients under treatment with any drug which can conceivably cause agranulocytosis. H. F.

The Schönlein-Henoch Syndrome. Yonis, Z., and Lerman, P.: Harefuah **59**: 9, 1960.

Twenty-two cases of Schönlein-Henoch syndrome hospitalized in Israel between 1951 and 1959 were analyzed. There were 11 boys and 11 girls in the group, and their ages ranged from 2½ to 11 years. All the children had abdominal pains and purpura and most of them also had arthralgia. Recurrences were few and of short duration and there were no readmissions. A few patients had a history of a preceding upper respiratory infection. There were no seasonal variations in morbidity. Five cases with some special features are discussed in greater detail. I. G.